REMARKS

Claims 1 and 3-9 are pending in the application and have been rejected.

Claim Rejections – 35 USC §103

Claims 1 and 3-9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Hutchinson (US 5,889,110) in view of Chen et al (US 7,081,489), Bhagwatwar et al (US 2003/0049320) and Yeh et al (US 5,869,103), cited by International Authority in related PCT Search Report.

The present invention provides a method for the preparation of nano- or microparticles, wherein an active substance is embedded in a polymer matrix by precipitating the active substance in a solution containing the polymer, and subsequently solidifying the polymer. The method is different from prior art techniques, because instead of adding the active substance in a solid state to the polymer solution, the active substance particles are formed in situ in the polymer solution. This precipitation and particle formation of the active substance takes place in a solution wherein the polymer is still dissolved in an organic solvent. The polymer is only then solidified to form the suspension of nano- or microparticles containing the precipitated active substance.

This unique and simple in situ precipitation and encapsulation method provides distinct advantages. The present method does not require that the active ingredient goes through a potentially harsh and disruptive drying cycle. Advantageously, the present process does not require sophisticated drying techniques, such as freeze drying techniques, to prepare the active substance. Additionally the present invention provides a system wherein a unique interaction of components is achieved through the order of precipitation of the active substance in the presence of the polymer in solution. By the sequential precipitation of the active substance by manipulation of solvents, followed by solidification of the polymer, formation of nano- or microparticles containing an active substance embedded in a polymer matrix is carried out by a convenient and economical process. Moreover, by forming the nano or micro particles containing an active substance

in a finely dispersed solid form in the presently claimed manner, negative effects of shear forces on the active substance can be avoided (cf. page 3, lines 15-20 of the present application). Finally, the present method provides a system wherein a unique interaction of components can be achieved through precipitation of the active substance in solution in the presence of the polymer.

The cited prior art does not teach or make obvious a method where i) an active substance is dissolved in a first solvent, ii) the first solution containing the dissolved active substance is mixed with a second solution having a dissolved polymer so that by the mixing of the first and second solutions the active substance is precipitated to form a suspension, and iii) then the polymer is solidified to form nano- or microparticles containing the precipitated active substance.

Briefly, the cited prior art fails to make the present invention obvious as follows: Hutchinson falls short of the present method, because he freeze-dries the active ingredient and adds it to the second solvent in dry form (Claim 16, step iv). Chen similarly dries the iron oxide particles, modifies the particles with surfactant in water, dries the particles again, and then adds them to a polyethylene-containing solution. Bhagwatwar does not contemplate precipitation of the active ingredient, but rather provides delivery of solvated drugs in a gelled polymer droplet-in-oil dispersion. Likewise, Yeh does not contemplate precipitation of the active ingredient.

The teachings of these references will now be discussed in more detail:

Hutchinson discloses salts composed of a cation derived from a peptide containing at least one basic group and an anion derived from a carboxy-terminated polyester, processes for the manufacture of such salts, and the use of such salts in the manufacture of extended release pharmaceutical compositions (i.e. microparticles). See the Abstract. The process of making such microparticles is detailed, for example, in claim 16, which states:

> 16. Microparticles comprising a composition consisting essentially of a salt formed from a cation derived from a peptide containing one or more basic groups and an anion derived from a carboxy-terminated polyester,

which composition has been prepared from at least an approximately stoichiometric equivalent of said polyester carboxylic acid end groups relative to said basic peptide groups, obtainable by a process comprising

i) dissolving the basic peptide and carboxy-terminated polyester in a first solvent in which both the peptide and the polyester are soluble to form a first solution;

ii) freezing said first solution at high speed to form a frozen mixture;

iii) freeze-drying the frozen mixture to remove said first solvent, forming a freeze-dried product;

iv) dispersing the freeze-dried product into a second solvent which is a solvent for the polyester and a non-solvent for the peptide to form a second solution containing said peptide/polyester salt; and

v) removing said second solvent from said second solution by a procedure selected from the group consisting of spray-drying, spray-congealing, evaporation and phase separation coacervation to form a solid product which is in the form of microparticles, or from which said microparticles are thereafter formed.

(emphasis provided)

Note that the first solvent and the second solvent of Hutchinson are never together in the same solution. The first solvent is removed in step iii) before the second solvent is introduced in step iv). Thus, it is impossible for Hutchinson to carry out an essential step of the presently claimed method. In the present method, the active substance is precipitated through solvent manipulation by combining a solution of an active substance dissolved in a smaller amount of a first solvent L1 with a solution of a polymer in a larger amount of a second organic solvent L2. The solvent L2 dissolves the polymer but is a non-solvent for the active substance. Upon mixing of these compositions, the active substance is precipitated and suspended in a solution comprising the polymer. As noted above, this precipitation by manipulation of solvent ratios is significant in providing a gentle and efficient precipitation process, and provides advantages that cannot be achieved by the prior art methods.

Turning to Chen, it is noted first that the cited patent, *per se*, is not available as prior art. The Chen patent application was filed August 8, 2002, and claims a priority date of August 9, 2001 from a prior filed US provisional patent application. The cited disclosure was not published until August 7, 2003. In contrast, the present application is entitled to a priority of March 15, 2002 through an EP priority document. The Chen patent disclosure is different from the disclosure of the priority provisional patent application, and therefore only the subject matter disclosed in the provisional patent application may be cited against the present application. Nevertheless, neither the Chen Patent nor the provisional application to which it claims priority discloses addition of the active substance to the polymer solution in a form other than the solid state. Contrary to the assertion in the Office Action, the "active substance" iron oxide of Chen is added to the polymer solution in a dry, solid powder form (cf. Provisional, page 6, lines 19 and 20 as well as the patent, col. 10, lines 14 to 16).

Therefore, there is no prior art teaching or suggestion of in-situ precipitation of an active agent in a polymer solution prior to its encapsulation in this polymer. Even in combination, the references teach the skilled artisan to add the active substance to the polymer solution in dry form.

The gap between Hutchinson and Chen and the present invention is not bridged by Bhagwatwar et al or Yeh et al.

Bhagwatwar is cited for its disclosure of forming microparticles comprising the elected species of active substance goserelin acetate and polymer poly-DL-lactide-co-glycolide with any suitable solvent. Bhagwatwar, however, does not contemplate precipitation of the drug in the polymer solution prior to solidifying the polymer, as is required in the present claims. Bhagwatwar does not add anything to the disclosure of Hutchinson relative obviousness of the present claims.

Yeh is cited for its disclosure of formation of nano/microparticles comprising active substances and poly-DL-lactide-co-glycolide. However, as in Bhagwatwar, the active agent of Yeh is provided in a solution, emulsion or suspension that is mixed with the polymer solution. A third solvent is mixed with this solution to precipitate the polymer

and form the microspheres. See column 4, lines 35-50. Thus, there is no teaching or suggestion of precipitation of the active agent in the polymer solution prior to solidifying the polymer, as is required in the present claims.

On careful review, it is clear that neither of the cited ancillary references are concerned with precipitation of active substances, let alone in the specific manner as it is claimed in the present claims. Reconsideration and withdrawal of the outstanding rejection is therefore respectfully requested.

Claim Rejections – 35 USC § 112 2nd

Claims 1 and 3-9 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action states that it is unclear what agents are contemplated as L1 and L2, and urges that the specification does not provide guidance as to the identity of solvents L1 and L2.

It is respectfully submitted that the specification provides ample guidance in understanding the fundamental nature of the solvents L1 and L2 to the skilled artisan at page 7, lines 9-10 and 24, and originally presented claim 2. Thus, L1 is a solvent that dissolves the active substance, L2 is a solvent that dissolves the polymer, and L2 also is a solvent in which the active substance is not soluble. Measurement of these physical properties for any given solvent and active ingredient is extremely routine, and can be carried out by any lab assistant in the art. Extensive technical teaching on selection of solvents based on solubility parameters is additionally provided at page 8, line 17 to page 9, line 7. Additionally, specific examples of solvents are provided in the specification at page 10, lines 11-22. Highly directed teaching of solvent selection, including many specific examples, is provided at page 10, line 28 to page 11, line 20. Specific formulation examples are presented in the present specification at page 13, line 6 to page 18, line 29.

Armed with this extensive teaching, the skilled artisan is well aware of the relationship of the solvents to each other, and clearly understands when they are practicing the present invention.

It is respectfully submitted that the plain meaning of the language of the claims is clear on its face to the skilled artisan, particularly in view of the extensive teaching provided by the present specification.

Conclusion

In view of the above amendments and remarks, it is respectfully submitted that the foregoing is fully responsive to the outstanding Office Action. Examination of all claims together, and early favorable consideration and passage of the above application to issue is earnestly solicited. In the event that a phone conference between the Examiner and the Applicant's undersigned attorney would help resolve any issues in the application, the Examiner is invited to contact said attorney at (651) 275-9811.

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Respectfully Submitted,

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